Based on Applicants' review of items 5 and 6 of the Official Action, it would appear that the rejections of the claims are primarily based upon the Examiner's concern that the claims encompass embodiments which are not enabled and in possession of the inventors at the time the application was filed. Specifically, the Examiner believes that the specification does not support ***any*** *isolated compound which prevents or treats an allergy and consists of (a) at least one of* ***any*** *allergen antigenic determinant which is recognised by a B cell or* ***any*** *antibody secreted by a B cell of a non-atopic individual to said allergen and (b) at least one of* ***any*** *antigenic determinant of an antigen different from said allergen which triggers T cell activation.* The Examiner believes that there is insufficient guidance and working examples in the specification to teach one skilled in the art how to make, use and be in possession of such compounds encompassed by the claims.

To address the Examiner's concerns and to simplify the examination of the present application, Applicants have amended claim 18 to specifically recite that the allergen is "Der pI and Der pII of house dust mite *Dermatophagoides pteronyssinus*". This amendment is presented without prejudice and should not imply that the now excluded but previously claimed subject matter is unpatentable. Applicants intend to file a new patent application for the now excluded subject matter in the near future.

Further, to demonstrate that there is sufficient guidance and working examples in the specification to teach one skilled in the art how to make, use and be in possession of the claimed invention, Applicants have prepared and filed a Rule 1.132 Declaration. The Declaration contains examples which confirm the immunogenicity of the construction made from a B cell epitope from an allergen linked to a T cell epitope from a different origin. This immunogenicity can be

demonstrated both for DNA immunization as well as for synthetic peptides, with a preferential increase in IgG2a antibodies in the first case. Further, the data indicate that findings similar to those obtained in the mouse can be observed in Der pII allergic individuals.

It should be noted that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983); see also In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404.* The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214. 219 (CCPA 1976).* As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).*

Further, it should also be noted that possession of the claimed invention is shown by describing the invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines Inc. 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).*

Applicants believe that from the amount of direction provided by the inventors in the specification, the existence of working examples (SEQ ID NOs:1, 3, 4 and 5) in the specification, and the teachings of the specification and claims, the present invention complies with the enablement and written description requirements of 35 U.S.C. § 112, first paragraph.

As disclosed in Applicants response of September 20, 2001, the claimed compound consists of two parts, a universal T cell epitope and a allergen-derived B cell epitope which adequately and clearly describe the claimed invention. The T cell epitope used in Examples 1-3 of the specification is an universal epitope which is known to be recognized by human beings after vaccination with tetanus toxoid (*see Panina-Bordignon et al., "Universally immunogenic T cell epitopes: promiscuous binding to human MHC class II and promiscuous recognition by T cells", Eur J. Immunol.1989, 19:2237,* previously submitted). In other words, the T cell moiety included in the claimed compound used to treat allergic diseases *is well recognized by allergic and non-allergic subjects*.

Further, it has also been shown based on the teachings of the specification that antibodies made by non-atopic individuals recognize preferentially sequential epitopes scattered over the entire molecule as compared to allergen-sensitive individuals producing antibodies towards conformational and discontinuous epitopes. It therefore follows that ***virtually any sequential epitope on an allergen that is no part of a conformational epitope can serve for the production of a compound suitable for administration, provided that the epitope is located in a random coil region of the protein and/or is readily accessible for antibody binding at the surface of the allergen molecule.***

Based on the knowledge in the art, the 3-D structure of the allergen Der pII has been elucidated (*see Mueller GA et al., "Tertiary structure of the major house dust mite allergen Der p 2: sequential and structural homologies", Biochemistry 1998, 37: 12707-12714,* previously submitted). Mice belonging to different genetic backgrounds produce antibodies towards peptide

11 to 35 of the Der pII region (*see Wu B. et al., "Major T cell epitope-containing peptides can elicit strong antibody responses", Eur J. Immunol 2000, 30: 291,* also previously submitted). The experiments shown in Figure 3 of the patent application clearly show that non-allergic individuals recognize the same Der pII region. Thus, the physico-chemical characteristics of the 15-35 region of Der pII and the fact that this region is recognized by all mouse strains and non-allergic individuals makes it highly likely that ***atopic patients injected with a claimed compound containing at least part of this region will produce antibodies specific to it, which will then cross-react with the native full-length Der p 2 allergen***.

The claimed compound used for therapy should not be recognized by IgE, antibodies made by allergic individuals, so as to avoid any risk of anaphylactic reaction. Figure 2 of the patent application already shows that IgE of Der pII allergic individuals do not bind to synthetic 12-mer peptides covering sequence 7 to 39. Thus, it can be clearly concluded that ***region 21-35 is not recognized by IgE antibodies even when 21-35 is presented in the form of a polypeptide, which allows conformation-dependent epitopes to be created.***

The claimed compound for use as an immunotherapeutic agent directs antibody production towards a discrete region of the molecule to the detriment of antibodies generated towards other epitopes (see Figure 1 of the patent application) which means that such focalization results in a very significant reduction in the production of IgE antibodies towards the native full-length allergen. In other words, IgG antibodies elicited towards the compound can inhibit the binding of IgE antibodies directed towards distant epitopes of Der pII. Since it is anticipated that patients will produce antibodies towards the claimed compound, ***such antibodies would also be***

able to inhibit the binding of human IgE antibodies to epitopes located at a distance of region 21-35.

From the teachings and experiments described in the specification using Der pI and Der pII (which are two main allergens of the house dust mite, *D. Pteronyssinus*), it has been shown that peptides, which fulfil the criteria of the present claims, can be easily identified and possessed by one skilled in the art without undue experimentation and that therapeutically active compounds based on such peptides for allergies can be prepared and obtained. In addition, the experimental data provided by the enclosed Rule 1.132 Declaration further support such a result.

Thus, Applicants submit that there is sufficient guidance and working examples in the specification to teach one skilled in the art how to make, use and be in possession of the compounds encompassed by the claims. In other words, Applicants believe that the representative examples in the specification and in the Rule 1.132 Declaration support the genus recited in the newly amended claims.

With regard to the rejection of claims 18-28 under 35 USC § 102(b) as being anticipated by Bixler et al (USP 5,785,973), this rejection is deemed to be untenable and is thus respectfully traversed.

To constitute anticipation of the claimed invention, a single prior art reference must disclose each and every material element of the claim which, in this case, Bixler et al. have failed to do.

Bixler et al. describe conjugates made of antigens, antigenic determinants of hapten with a T-cell epitope of a bacterial product (see column 5, lines 42-44, of the reference). The coupling of

the full length allergen is also reported and few examples of possible allergens are provided (see column 8, lines 27-28 and column 12, lines 53-74 of the reference). Further, the reference also mentions that the term "antigen" means either the whole antigen or one of its determinants (see column 12, lines 10-11). However, all the claims of Bixler et al. (see column 35, line 63) deal with **polysaccharide antigens** only.

In contrast, the peptides according to the present invention are derived from **allergen only** and are ***never glysosylated***. Further, the compound according to the present invention also differs from wild-type sequences by one or more amino acid substitutions aiming at eliminating a T-cell epitope (said aspect being a preferred embodiment of the present invention).

It also must be note that Bixler et al. neither describe nor suggest the use of an isolated compound for preventing or treating an allergy, said compound consisting of at least one allergen antigenic determinant which is recognised by a B-cell (or an antibody secreted by a B-cell) **of an non-atopic individual to said allergen** and one allergen antigenic determinant of an antigen different from said allergen which triggers T-cell activation.

Thus, since Bixler et al. fail to teach or suggestion all of the limitations of the claims, this rejection can no longer be sustained and should be withdrawn.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

In view of the foregoing amendments and remarks, it is respectfully submitted that the Application is now in condition for allowance. Such action is thus respectfully solicited.

If, however, the Examiner has any suggestions for expediting allowance of the application or believes that direct communication with Applicants' attorney will advance the prosecution of this case, the Examiner is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

The claims have been amended as follows:

18. (Amended) An isolated compound for preventing or treating an allergy, said compound consisting of (a) at least one allergen antigenic determinant which is recognised by a B cell or an antibody secreted by a B cell of a non-atopic individual to said allergen and (b) at least one antigenic determinant of an antigen different from said allergen which triggers T cell activation, wherein said allergen is Der pI and Der pII of house dust mite *Dermatophagoides pteronyssinus*.

29. (Amended) The compound according to claim 18, which comprises one of the following amino acid sequences selected from the group consisting of SEQ ID NO. 1, [SEQ ID NO. 2,] SEQ ID NO. 3, SEQ ID NO. 4 and SEQ ID NO. 5.